C2

1. **(Twice amended)** A method for treating cancer in a mammal, comprising:

isolating an urine isolate comprising a pool of molecules larger than about 1000 daltons from a mammal with cancer; and

administering an effective amount of the urine isolate by injection to said mammal with cancer.

C3

72. **(Amended)** The method of Claim 1, wherein the urine isolate is administered within exosomes.

C4

77. **(Amended)** The method of Claim 20, wherein the urine isolate is administered within exosomes.

REMARKS

Claims 1-34 and 70-79 remain presented for examination. No new matter has been added by this amendment. The Examiner requested the removal of the language "BCG" from the paragraph inserted by amendment in the first amendment dated August 8, 2002. The paragraph has now been amended as requested. Applicants note that BCG is an immune-stimulating compound known in the art and, as such, methods involving BCG would be encompassed within the scope of several claims such as, for example, Claim 16. Further, minor spelling errors in Claims 72 and 77 have been corrected by this amendment: the incorrect word "siolate" has been replaced with the correct word "isolate."

Rejections Under 35 U.S.C. § 112

As a preliminary matter, Applicant notes that the present Office Action introduces, for the first time, several rejection under 35 U.S.C. § 112. There were no such rejections in the first Office Action. Piecemeal examination is officially discouraged by the PTO. MPEP 707.07(g). The piecemeal approach of the instant examination is exacerbated by the lack of merit in the instant rejections under § 112. In light of the fact that the first Office Action did not find any basis for rejection of any of the claims under § 112, and in light of the following arguments, Applicant respectfully requests withdrawal of all rejections under § 112.

Discussion of Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-34, 70-79 are rejected under U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention.

The Examiner rejected Claims 1 and 20 under U.S.C. § 112, second paragraph, citing that the metes and bounds of the phrase "an effective amount" is not clear. While a large range of amounts may be suitable for effectively treating cancer using the method of the invention, the specification teaches sample guidelines. Example 1 (page 10, line 29 to page 11, line 4) teaches that 1,000 to 10,000 ml of urine is collected from the patient. After the removal of low molecular weight (<1,000 Daltons) molecules, the retentate is used as a vaccine (page 11, line 4). One of skill in the art would be able to make and use the invention using these guidelines. Therefore, the metes and bounds of both Claims 1 and 20 are clearly understood from a reading of the specification.

The Examiner further rejected Claim 20 under U.S.C. § 112, second paragraph, for the language "sterile urine isolate." The examiner alleged that the specification does not teach the method of sterilization of the urine isolate. However, one of skill in the art would readily understand and be able to apply sterile techniques that are routinely used in clinical or laboratory environments. For example, 0.2 micron filters are typically used for removal of whole bacterial cells. The urine may be filtered with this 0.2 micron filter immediately, or the filtration may take place any time before injection into the patient. One of skill in the art would also understand basic sterilization methods for keeping the isolate sterile (for example, by using sterilized containers or by using a sterile working environment such as a sterile hood or sterile room). Of course, the urine itself may be free of bacterial contamination when it is provided from the patient, and may require no other treatment than to be processed and stored in a sterile manner.

The Examiner additionally rejected Claim 70 under U.S.C. § 112, second paragraph, citing that the metes and bounds of the phrase "an effective amount" is not clear. The Examiner alleged that the specification does not teach the amount of dendritic cells required to be "an effective amount." However, Example 6 at page 13, lines 8 - 9 teaches the use of "80 ml of peripheral blood from the same patient and expanded as described in Example 3." Example 3 describes the method of expanding the dendritic cell population. One of skill in the art could start with 80 ml of patient blood as taught in example 6, then expand the dendritic cell population as clearly described in Example 3, then reinfuse all or part of the pulsed dendritic cell population

to the patient. Examples 9-18 also teach the use of weekly injections of from 4 to 12 weeks prior to testing for effectiveness. Therefore, the metes and bounds of the phrase "an effective amount" of Claim 70 can be clearly understood from a reading of the specification.

Accordingly, the withdrawal of the rejection of Claims 1, 20, and 70, based on U.S.C. § 112, second paragraph, is requested.

Discussion of Rejection under 35 U.S.C. § 112, first paragraph

Written description:

Claims 70-79 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. It appears that the Examiner has objected to the term "antigen presenting cells" (APCs) in the specification and the claims.

APCs are known in the art, and APCs are clearly mentioned in the specification and in the original claims. There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). MPEP 2163. Persons of skill in the art know what APCs are, and would recognize that Applicant's use of this term in the specification and the original claims indicates his posession of the claimed subject matter at the time of filing. Thus the claims are supported by adequate written description, the PTO has not met its burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims, and the rejection should be withdrawn.

Enablement:

Claims 1-19 and 70-79 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These rejections, and the Examiner's arguments in support thereof, are improper and are inconsistent with the guidelines proffered by the PTO.

The Examiner admits that the specification gives several examples of cancer status being improved, but improperly dismisses all of these examples are merely anecdotal. This ignores the

fact that the specification could be enabling without even a single example of success in humans. The Examiner admits that treatment of cancer is not a trivial matter, but then trivializes the significant successes disclosed in the specification by dismissing them as anecdotes from which one cannot extrapolate.

The Examiner has impropery issued an enablement rejection as a proxy for a utility rejection. The Examiner clearly believes, and states, that "no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer." Thus, the Examiner does not accept the assertion of utility; however, in maintaining this position, it is necessary for the Examiner to ignore multiple examples of utility.

The actual practice of the invention as claimed is exceedingly simple, as the specification points out. Yet the Examiner asserts that "phase I, II, and III human clinical trials is required in order to practice the invention." This assertion is plainly inconsistent with the Utility Guidelines: "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials." MPEP 2107.03.

Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). "To be enabling, the specification of a patent must teach those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation' ... Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *See In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993).

Regarding Claims 1-19, the specification clearly and adequately describes how to prepare the urine isolate for administration (see Example 1). Regarding Claims 70-79, the specification clearly describes how to prepare the dendritic cells, how to expand the dendritic cell population, how to pulse the dendritic cells with the urine isolate, how to administer the composition to the patient, and finally how to observe the effectiveness of the treatment. Therefore, the specification adequately teaches those of skill in the art how to make and use the invention. Accordingly, the withdrawal of the rejection of Claims 1-19 and 70-79, based on U.S.C. § 112, first paragraph, for lack of enablement, is requested.

The Examiner also rejected Claims 20-34 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner appears to believe that the specification does not teach an enabling

method of treating cachexia using autologous urine isolate. The Examiner further cites that there are no examples stating that the patient was administered urine isolate to treat cachexia.

However, the use of urine isolate for treating cachexia in addition to cancer is clearly taught in the specification:

> *"The high molecular weight isolate from the urine of the mammal contains organism-specific tumor associated antigens and cachexia-inducing molecules, which, when injected into an immunogenic organ such as the skin, with or without an adjuvant will result in an immune response against the antigen and against the molecules that cause cachexia."* (page 5, line 28 through page 6, line 1).

Further, as described earlier, Example 1 describes how to prepare the urine isolate. Example 1 at page 11, lines 3-5 states that "the retentate was then used as a vaccine...." Thus, the method for using urine isolate alone, without being pulsed to dendritic cells, for administration to a patient is demonstrated. Because the Example is entitled "isolation of HIU" (rather than being limited to a cancer treatment or cachexia treatment), it is clear that Example 1 teaches the use of urine isolate for both treatment of cancer and for treatment of cachexia. Accordingly, the withdrawal of the rejection of Claims 20-34, based on U.S.C. § 112, first paragraph, for lack of enablement, is requested.

Discussion of Rejection Under 35 U.S.C. § 103

The Examiner rejected Claims 1, 2, 6, 7, 16, 17, 19, and 70-79 under 35 U.S.C. § 103(a) as being unpatentable over Eldor in view of Voet.

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art must reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Claims 1, 2, 6, 7, 16, 17, 19, and 70-79 are not obvious over Eldor in view of Voet because neither of the references provides a motivation to combine or modify the teachings of Eldor to achieve the claimed invention.

Eldor teaches the use of oral administration of one's own urine as a cancer treatment. Eldor does not teach any other means of administration other than oral. Further, there is no

discussion that urine is in any way deleterious. Nor does Eldor teach or suggest that urine should be treated to remove toxins or materials of less than 1,000 Daltons before administration.

Voet teaches that in mammals, excess nitrogen (formed from the breakdown of amino acids) is excreted in urine in the form of urea. Voet does not teach that urea would be deleterious if injected. Voet does not teach that the toxic compounds in urine are of < 1,000 Daltons. Further, Voet does not teach that urine would no longer be toxic (i.e., would be suitable for injection into a patient) upon removal of the 1,000 Dalton fraction.

Voet simply teaches that excess nitrogen forms urea and leaves the vertebrate body in the urine.

Claims 1, 2, 6, 7, 16, 17, 19, and 70-79 are not obvious over Eldor in view of Voet because the references do not provide a reasonable expectation of success. Urine is generally considered to be a waste product to be eliminated from the body. Thus, one would assume that deleterious molecules present in the urine would be of various sizes, rather than just <1,000. Therefore, it would not be obvious that the urine isolate would be suitable for injection to a cancer patient after simply removing the < 1,000 fraction.

Claims 1, 2, 6, 7, 16, 17, 19, and 70-79 are not obvious over Eldor in view of Voet because the cited references do not contain all of the limitations of the claimed invention. The Eldor reference does not discuss removing anything from the urine to be administered. Accordingly, Eldor et al does not contain any suggestion of the limitation "molecules larger than about 1,000 Daltons." Voet also does not contain such a limitation.

The specification teaches that several small molecules may be present in the low molecular weight fraction of urine:

> "*The low molecular weight components of urine are comprised of inorganic (salts, minerals, metals), nitrogenous compounds (urea, creatinine, creatine, guanidine, ammonia, alpha amino nitrogen, free amino acids, betaines, nitriles, aliphatic amines, aromatic amines, porphyrins and related products, purines and related compounds, nucleosides, cyclic nucleotides, uric acid, allantoin, and pyrimidines and related compounds), carbohydrates, lipids, organic acids, bile acids, prostaglandin, hormones, and vitamin molecules.*" (Page 7, lines 22-28).

The specification notes that most of these compounds have no tumor antigenicity, in fact, some of them may actually competitively inhibit the action of tumor-associated antigens.

Therefore, their removal would increase the concentration of any tumor antigens present in the urine isolate:

> *"Many of these molecules, which have no tumor associated antigenicity. In addition, they may competitively inhibit the interaction of unspecified tumor associated antigens found in the high molecular weight fraction of urine with the DCs and adversely affect the viability of the DCs at the time of pulsing. Therefore it is advantageous to remove these compounds."* (Page 7, line 28 to page 8, line 2).

Further, Claim 1, as now amended, contains the limitation that the urine isolate is to be administered by injection. Eldor does not teach nor suggest this limitation. Thus, the prior art does not teach all the limitation of the claims, as now amended.

As can be seen from the discussion above, the three-pronged test has not been met, and thus a *prima facie* case of obviousness cannot be established. In view of the amended claims and the above discussion, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 103, and allowance of the pending application.

The examiner further rejected Claims 3-5, 8-15, and 70-79 under 35 U.S.C. § 103(a) as being unpatentable over Eldor in view of Voet as applied to claims 1, 2, 6, 7 and further in view of Nestle and Zitvogel.

Claims 3-5, 8-15, and 70-79 are not obvious over Eldor in view of Voet as applied to claims 1, 2, 6, 7 and further in view of Nestle and Zitvogel because the cited references do not provide a motivation to combine or modify the reference to achieve the claimed invention. The Examiner asserts that Nestle teaches a diverse protein population. However, Nestle teaches merely the use of either 1) tumor cells that have been isolated from tumor tissue, and subsequently lysed to provide a tumor lysate, or 2) one of three small synthetically prepared peptides. The present invention, in contrast, teaches the use of a urine isolate containing a complex mixture of molecules (i.e., anything that is present in the urine after having the molecules of less than about 1,000 Daltons removed).

There is no suggestion or motivation in the cited references to modify the method of Eldor by removing molecules of less than 1,000 Daltons and no suggestion or motivation to inject such a composition to a patient as a cancer treatment.

Claims 3-5, 8-15, and 70-79 are not obvious over Eldor in view of Voet as applied to claims 1, 2, 6, 7 and further in view of Nestle and Zitvogel because the reference(s) do not

provide a reasonable expectation of success. Voet, Nestle, and Zitvogel teach only the use of specific proteins, specific peptides, or tumor lysates that are isolated and purified from a specific source, then the purified proteins themselves are used as antigen material for vaccine purposes. These do not suggest that injection of a pool of various molecules present in a crude isolate from urine, having only the 1,000 Dalton and lower fraction removed, would be in any way successful for treating cancer. Thus, a *prima facie* case of obviousness of Claims 3-5, 8-15, and 70-79 over Eldor in view of Voet as applied to claims 1, 2, 6, 7 and further in view of Nestle and Zitvogel can not be established.

For all of the above reasons, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 103(a), and allowance of the pending application.

Additional factors demonstrating unobviousness of the invention

Several additional factors further establish to the unobviousness of the invention. First, **the present invention contains an unsuggested modification** – it was not previously suggested that the method of Eldor could be modified by only removing the < 1,000 Dalton fraction, in order for the urine isolate to be suitable for injection to the patient.

Further, the present invention involves fewer preparation steps than that of the cited prior art. The methods of Nestle and Zitvogel involve complicated tumor isolation and processing steps, prior to the dendritic cell pulsing step. For example, Nestle involves the steps of surgery to isolate tumor tissue, removal of nonmalignant tissue from the tumor tissue, isolation of cells to create a single cell layer, vitality testing of the cells, cell counting, several freeze thaw cycles to lyse the cells, then centrifugation to remove the large particles, all prior to DC pulsing. The present invention, in contrast, requires only that urine be collected and the 1,000 Dalton fraction removed before administration to the patient (as in Claims 1-34) or before pulsing DCs (as in Claims 70-79). Multiple proteins (both tumor-associated and nontumor-associated) and other types of molecules may be present, with the proviso that they are larger than about 1,000 Daltons. The simple step of removing the <1,000 Dalton fraction is certainly less complicated than tumor surgery, cell isolation, vitality testing, and cell lysis of Nestle or Zitvogel. Thus, the present invention omits steps present in the cited prior art.

The present invention has several advantages over the cited prior art. The method is very simple, requiring no patient surgery and no complex protein purification or tumor isolation

procedures. The method of Claims 1-34, in particular, can even be performed outside of a laboratory stetting, using, for example, a portable, disposable filtration device. Since laboratory and clinical environments are typically very expensive to set up, the present invention has the remarkable advantage that it can be performed at very low cost, outside of a clinical environment (such as, for example, home use).

The present invention solves a long–felt need for a very inexpensive but effective cancer treatment method. Considering the current escalating costs of other cancer treatments, a simple yet elegant method such as this is clearly of great benefit.

Conclusion

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. Any claim amendments which are not specifically discussed in the above remarks are made in order to improve the clarity of claim language, to correct grammatical mistakes or ambiguities, and to otherwise improve the capacity of the claims to particularly and distinctly point out the invention to those of skill in the art. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested.

The specific changes to the specification and the amended claims are shown on a separate set of pages attached hereto and entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this Amendment. On this set of pages, the insertions are double underlined while the ~~deletions are stricken through~~.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: February 28, 2003

By: _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. A method for treating cancer in a mammal, comprising:

isolating an urine isolate comprising a pool of molecules larger than about 1000 daltons from a mammal with cancer; and

administering an effective amount of the urine isolate by injection to said mammal with cancer.

72. The method of Claim 1, wherein the urine isolate ~~siolate~~ is administered within exosomes.

77. The method of Claim 20, wherein the urine ~~siolate~~ isolate is administered within exosomes.